Trauma patients with hypokalemia have an increased risk of morbidity and mortality

Schlögl, Mathias ; Käch, Ilja ; Beeler, Patrick E ; Pape, Hans-Christoph ; Neuhaus, Valentin

Abstract: Introduction The aims of our study were (1) to determine the prevalence of hypokalemia, (2) to evaluate predictors for hypokalemia, and (3) to show the influence of hypokalemia on in-hospital outcome (mortality, adverse events, and length of stay) in a general trauma cohort. Methods We performed a four-year retrospective study and analyzed the influence of hypokalemia during hospitalization in all adult trauma patients admitted to a Level-1 trauma center. A total of 7692 consecutive trauma patients were included and further analyzed. We used multivariate regression analyses to examine the predictors for hypokalemia, mortality, adverse events, and length of stay while adjusting for covariates, including age, sex, injuries and comorbidities. Results Hypokalemia was present in 33% (n = 2565) of all adult trauma patients, with a peak at the first two days. Congestive heart failure (OR 2.2, $p < 0.001$) and head injury (OR 2.0, $p < 0.001$) were the most important risk factors for hypokalemia. Moderate to severe hypokalemia (<3.0mmol/L) was a significant predictor for mortality (OR 2.4, $p = 0.001$), while mild hypokalemia (3.0 – 3.5mmol/L) was not. Moderate to severe hypokalemia (OR 3.4, $p < 0.001$) and mild hypokalemia (OR 1.7, $p < 0.001$) were significant predictors for adverse events. Last, patients with hypokalemia stayed significantly longer in the hospital (13 ±9 days vs. 8 ±12, $p < 0.001$). Conclusions Trauma patients presenting with hypokalemia during hospitalization have an increased risk of dying and suffering adverse events and need special medical attention.

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Trauma patients with hypokalemia have an increased risk of morbidity and mortality

Mathias Schlögl [d], Ilja Käch [a], Patrick E. Beeler [b,c], Hans-Christoph Pape [a], Valentin Neuhaus [a,*]

[a] *Division of Trauma Surgery, University Hospital of Zurich, Switzerland*
[b] *Department of Internal Medicine, University Hospital of Zurich, Switzerland*
[c] *Division of General Internal Medicine, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA*
[d] *University Clinic for Acute Geriatric Care, City Hospital Waid, Zurich, Switzerland*

A R T I C L E I N F O

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A B S T R A C T

Introduction: The aims of our study were (1) to determine the prevalence of hypokalemia, (2) to evaluate predictors for hypokalemia, and (3) to show the influence of hypokalemia on in-hospital outcome (mortality, adverse events, and length of stay) in a general trauma cohort.
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Conclusions: Trauma patients presenting with hypokalemia during hospitalization have an increased risk of dying and suffering adverse events and need special medical attention.

Introduction

Potassium abnormalities are frequent problems in hospitalized patients. Especially hypokalemia is a common and neglected finding in our daily practice with trauma patients. Studies report up to 50% of trauma patients presenting with hypokalemia.[1-3]

Potassium abnormalities are associated with mortality and morbidity in surgical patients.[4, 5] Morell et al. showed in 156 trauma patients that hypokalemia was associated with an increased total length of stay.[6] Presence or development of hypokalemia in trauma patients during an intensive care unit stay was also associated with prolonged mechanical ventilation and thereby associated with significant morbidity and mortality.[7, 8] Further, severe hypokalemia was an independent risk factor for mortality in traumatic brain injured patients.[2, 9]

The clinical importance of the potassium level is also evident because of its use in some clinical scores, such as the Acute Physiology And Chronic Health Evaluation (APACHE II) score or the Simplified Acute Physiology Score (SAPS).[10, 11] Both, hypo- and hyperkalemia increase the scores and are associated with a reduced survival rate for intensive care unit patients.

The problems are, that most studies analyzed only small cohorts, included a special subgroup of trauma patients only, or did not distinguish the severity of hypokalemia. A better understanding of the plasma potassium level in the general trauma patient and the influence on in-hospital outcome might improve the specific monitoring and treatment and thereby reduce the risk for a negative outcome. The aims of our study were (1) to determine the prevalence of hypokalemia in trauma patients, (2) to evaluate trauma and comorbidities related

* Corresponding author at: University Hospital of Zurich USZ / Univeristy of Zurich UZH, Raemistrasse 100, 8091 Zuerich, Switzerland.
E-mail address: valentin.neuhaus@gmx.ch (V. Neuhaus).

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predictors for hypokalemia, and (3) to show the influence of hypokalemia on in-hospital outcome (mortality, adverse events, and length of stay) of a general and orthopaedic trauma cohort.

Methods

Study design

In this four-year retrospective study, we analyzed the influence of hypokalemia during hospitalization in all adult trauma patients at a Level I trauma center. This trauma center treats mainly orthopedic trauma patients, but also traumatic brain, chest, and abdominal injuries of adult patients. The cantonal ethical review board (KEK-ZH-No. 2011-0382, PB_2016_01888) approved this study.

Patients

Inclusion criteria were all adult trauma patients (older than 18 years) admitted to the trauma center between 2010 and 2014. To study the influence of potassium level on outcome, trauma patients had to be hospitalized three or more days (by authors' choice), and must have had at least one potassium level reported during hospitalization. Of 13891 trauma patients, 7692 (55%) met these inclusion criteria and were further analyzed (Table 1).

Comprehensive, routinely collected electronic health record data of all admitted trauma patients were available and analyzed, including (1) age, (2) sex, (3) admission from, (4) injuries, (5) comorbidities, (6) length of stay (LOS), (7) in-hospital death, and (8) adverse events. All injuries and comorbidities were ICD-10 codes [12] by professional medical coders. An adverse event was considered if the corresponding ICD-10 code of an acute disease was present, such as acute hemorrhagic anemia, urinary tract infection, respiratory insufficiency as well as pneumonia and unplanned intubation, acute renal failure, pulmonary embolus, thromboembolic events, cerebrovascular accidents, recent myocardial infarction, and similar diagnoses (Table 2).

Potassium

Plasma potassium was detected with ion selective electrodes by using COBAS 8000 modular analyzer series (Roche Diagnostics, USA), and the normal range of potassium in the blood plasma was considered to be between 3.6 – 5.2 mmol/l. Hypokalemia was defined as potassium level in the blood plasma < 3.6 mmol/L. For analyzing and calculating the predictors for mortality and complications as well as using linear

Table 1
Overview

		Total		Hypokalemia				P Value
		n=7692		no n=5127 (66%)		present n=2565 (33%)		
		n	%	n	%	n	%	
Age (years ± SD)		54	±21	53	±21	56	±21	<0.001
Sex	Female	3159	41%	1928	38%	1231	48%	<0.001
	Male	4533	59%	3199	62%	1334	52%	
Admission from	Home	6018	78%	4136	81%	1882	73%	<0.001
	Other hospital	1206	16%	697	14%	509	20%	
	Other	215	2.8%	139	2.7%	76	3.0%	
	Retirement home	80	1.0%	51	1.0%	29	1.1%	
	Nursing home	71	0.9%	42	0.8%	29	1.1%	
	Home with home health care	69	0.9%	38	0.7%	31	1.2%	
	Mental institution	27	0.4%	20	0.4%	7	0.3%	
	Prison	6	0.1%	4	0.1%	2	0.1%	
Comorbidities								
Hypertension		1655	22%	987	19%	668	26%	<0.001
Diseases of the musculosceletal and connective tissue system		1632	21%	1084	21%	548	21%	0.906
Mental disorders		1401	18%	718	14%	683	27%	<0.001
Cardiac arrhythmia		586	7.6%	339	6.6%	247	9.6%	<0.001
Diabetes mellitus		493	6.4%	325	6.3%	168	6.5%	0.766
Malignancy		453	5.9%	260	5.1%	193	7.5%	<0.001
Chronic pulmonary disease		257	3.3%	148	2.9%	109	4.2%	0.002
Cerebrovascular disease		234	3.0%	131	2.6%	103	4.0%	0.002
Chronic renal disease		234	3.0%	164	3.2%	70	2.7%	0.291
Thyroid disease		206	2.7%	128	2.5%	78	3.0%	0.227
Disorder of the lipometabolism		203	2.6%	129	2.5%	74	2.9%	0.364
Oesophagitis, GERD, peptic ulcer disease, gastritis, duodenitis		198	2.6%	86	1.7%	112	4.4%	<0.001
Coronary artery disease		170	2.2%	111	2.2%	59	2.3%	0.742
Occlusive peripheral artery disease		112	1.5%	78	1.5%	34	1.3%	0.545
Congestive heart failure		94	1.2%	40	0.8%	54	2.1%	<0.001
Injuries								
Extremity injury		4374	57%	3010	59%	1364	53%	<0.001
Head injury		2472	32%	1325	26%	1147	45%	<0.001
Thoracic injury		1274	17%	694	14%	580	23%	<0.001
Spinal column injury		1130	15%	633	12%	497	19%	<0.001
Abdominal injury		640	8.3%	316	6.2%	324	13%	<0.001
Pelvic injury		560	7.3%	289	5.6%	271	11%	<0.001
Length of stay (days ± SD)		10	±7	8	±12	13	±9	<0.001
Deceased		154	2.0%	85	1.7%	69	2.7%	0.004
Adverse events		2024	26%	1067	21%	957	37%	<0.001

Table 2
Negative in-hospital outcome

	No hypokalemia		Mild hypokalemia		Severe hypokalemia		P Value
	(3.6-5.2mmol/L)		(3.0-3.5mmol/L)		(<3.0mmol/L)		
	n	%	n	%	n	%	
Deceased	**85**	**1.7%**	**47**	**2.1%**	**22**	**6.1%**	<0.001
Adverse events	**1067**	**21%**	**759**	**34%**	**198**	**55%**	**<0.001**
Complications of operations	523	10%	308	14%	80	22%	<0.001
- Complications due to endoprothesis, implants, transplants	194	3.8%	80	3.6%	12	3.4%	0.89
- Wound/ procedure complications	181	3.5%	127	5.8%	38	10.6%	<0.001
- Postoperative wound infection	91	1.8%	64	2.9%	17	4.8%	<0.001
- Hematoma/ seroma	84	1.6%	63	2.9%	15	4.2%	<0.001
- Wound dehiscence	23	0.4%	16	0.7%	10	2.8%	<0.001
Acute hemorrhagic anemia	213	4.2%	223	10%	44	12%	<0.001
Urinary tract infection	195	3.8%	148	6.7%	48	13%	<0.001
Intubation	136	2.7%	165	7.5%	57	16%	<0.001
Pneumonia	111	2.2%	115	5.2%	58	16%	<0.001
Determined early complications of a trauma	92	1.8%	72	3.3%	21	5.9%	<0.001
Respiratory insufficiency	62	1.2%	59	2.7%	19	5.3%	<0.001
Systemic inflammatory response syndrome	61	1.2%	60	2.7%	24	6.7%	<0.001
Sepsis	52	1.0%	40	1.8%	19	5.3%	<0.001
Traumatic muscle ischemia	51	1.0%	54	2.4%	17	4.8%	<0.001
Acute renal failure	45	0.9%	33	1.5%	12	3.4%	<0.001
Aspiration pneumonia incl. Mendelson-syndrome	34	0.7%	46	2.1%	21	5.9%	<0.001
Deep vein thrombosis	23	0.4%	23	1.0%	9	2.5%	<0.001
Pulmonary embolism	22	0.4%	27	1.2%	7	2.0%	<0.001
Withdrawal symptoms with delirium	19	0.4%	20	0.9%	4	1.1%	0.002
Recent myocardial infarction	17	0.3%	9	0.4%	3	0.8%	0.301
Reanimation	17	0.3%	9	0.4%	3	0.8%	0.257
Cerebral infarction (thrombosis or embolism)	16	0.3%	14	0.6%	8	2.2%	<0.001
Complications after therapeutic infusions, transfusions or injections	7	0.1%	9	0.4%	2	0.6%	0.074
Disseminated intravascular coagulation disorder	0		7	0.3%	3	0.8%	<0.001

regression for length of stay, we stratified potassium into categories of “no hypokalemia”, “mild” (3.0 – 3.5 mmol/L) and “moderate or severe” (< 3.0 mmol/L) hypokalemia.[13]

Statistical analyses

The outcomes were presence of hypokalemia during hospitalization, length of stay, in-hospital mortality, and presence of any adverse events. We used logistic regression analyses to examine the predictors for hypokalemia, mortality and adverse events while adjusting for covariates, including baseline differences in age, sex, injuries and comorbidities (all included injuries and comorbidities are presented in Table 1). The odds ratio (OR) and 95 % confidence interval (CI) of the logistic regression analyses results are reported. Linear regression analyses were used to investigate the significant predictors for length of stay. Statistical analyses were performed using IBM SPSS Statistics (Version 22, IBM SPSS, Chicago, IL, USA). Significance was accepted at $p < 0.005$ because of multiple testing.[14] Data are presented as mean ± standard deviation (SD) or median (inter-quartile range). Categorical variables are described as absolute (n) and relative (%) frequencies.

Results

Prevalence of and risk factors for hypokalemia

In the first blood analysis, 17.5% (n = 1346) of the patients had a hypokalemia. Hypokalemia, anytime during the hospitalization, was present in 33.3% (n = 2565). A total of 2591 patients had two or more blood analysis. A persistent or recurrent hypokalemia was present in 11% (n = 285).

Independent risk factors for hypokalemia were distinct comorbidities (congestive heart failure, gastro-esophageal reflux disease, mental disorder, and malignancy), certain injuries (head, abdominal, pelvic, spine, and chest), and female sex. Chronic renal disease had an odds ratio of 0.6 (95% CI 0.44-0.82). The model explained 12% of the variation (R^2 = 0.12) (Table 3).

Outcome measures

Overall *mortality* rate was 2.0%; 6.1% in the group with severe, 2.1% in the group with mild, and 1.7% in the group without hypokalemia ($p < 0.005$) (Table 2). There was no correlation between the mortality rate and the time between admission and the detection of the hypokalemia (e.g. day 1 2.7% vs. day 2-8 2.6% vs. day 9 or later 2.7%, p=0.802). Severe hypokalemia was a significant mortality predictor (OR 2.4, 95% CI 1.4 – 4.0, p = 0.001) while mild hypokalemia (OR 1.04, 95% CI 0.71 – 1.52, p = 0.831) was not. Distinct comorbidities such as congestive heart failure, cerebrovascular disease, and cardiac arrhythmia were further significant predictors for mortality. In addition, significant predictors for mortality were thoracic and head injury, age, and sex (male). The model explained 20% of the variation (R^2 = 0.203) with a good accuracy (AUC = 0.859) (Table 4).

Table 3
Predictors for hypokalemia

	P Value	OR	95% CI	
Congestive heart failure	**<0.001**	2.2	1.4	3.4
Oesophagitis, GERD, peptic ulcer disease, gastritis, duodenitis	**<0.001**	2.1	1.6	2.9
Head injury	**<0.001**	2.0	1.8	2.3
Mental disorder	**<0.001**	1.7	1.5	2.0
Sex (Female)	**<0.001**	1.6	1.5	1.8
Abdominal injury	**<0.001**	1.6	1.3	1.9
Malignancy	**<0.001**	1.5	1.2	1.8
Pelvic injury	**<0.001**	1.4	1.2	1.7
Spinal column injury	**<0.001**	1.3	1.1	1.5
Thoracic injury	**0.001**	1.3	1.1	1.5
Hypertension	0.006	1.2	1.05	1.3
Extremity injury	0.011	0.87	0.78	0.97
Chronic renal disease	**0.001**	0.60	0.44	0.82

CI, confidence interval; GERD, gastro-esophageal reflux disorder, OR, odds ratio

Table 4
Predictors for mortality

	P Value	OR	95% CI	
Congestive heart failure	**<0.001**	4.1	2.1	7.8
Cerebrovascular disease	**<0.001**	3.7	2.3	6.0
Thoracic injury	**<0.001**	2.7	1.8	3.8
Severe hypokalemia	**0.001**	2.4	1.4	4.0
Cardiac arrhythmia	**<0.001**	2.3	1.5	3.5
Sex (Male)	**<0.001**	2.2	1.5	3.2
Head injury	**<0.001**	2.1	1.4	2.9
Malignancy	0.026	1.8	1.1	3.1
Pelvic injury	0.017	1.8	1.1	2.9
Chronic renal disease	0.047	1.8	1.0	3.1
Mild hypokalemia	0.831	1.0	0.7	1.5
Age	**<0.001**	1.035	1.024	1.046

CI, confidence interval; OR, odds ratio

Overall *adverse event* rate was 26%; 55% in the severe hypokalemia group, 34% in the mild hypokalemia group, and 21% in the group without hypokalemia ($p < 0.001$) (Table 2). The most often encountered adverse events were complications of operations (e.g., surgical site infection, local hematoma), unplanned intubation, pneumonia as well as urinary tract infection. The later a hypokalemia was detected, the higher was the adverse event rate (e.g. day 1 26.4% vs. day 2-8 38.0% vs. day 9 or later 63.8%, $p < 0.001$). Significant predictors for adverse events were severe hypokalemia (OR 3.4, 95% CI 2.7 – 4.4, $p < 0.001$), mild hypokalemia (OR 1.7, 95% CI 1.5 – 1.9, $p < 0.001$), gastro-esophageal reflux disease, cardiac arrhythmia, mental disorder, chronic pulmonary disease, certain injuries (pelvic, chest, abdomen, spine), age and male sex. The model explained 17% of the variation ($R^2 = 0.17$) with a fair accuracy (AUC = 0.717) (Table 5).

Patients with hypokalemia stayed significantly longer (13 ±9 days vs. 8 ±12 days in the group with normal potassium levels; $p < 0.001$) (Table 1). Predictors for *length of stay* were hypokalemia ($p < 0.001$), comorbidities such as cardiac arrhythmia, congestive heart failure, chronic pulmonary disease, gastrointestinal disease, and obesity, distinct injuries (chest, abdomen, pelvic and spine), as well as age and male sex (Table 6).

Table 5
Predictors for adverse events

	P Value	OR	95% CI	
Severe hypokalemia	**<0.001**	3.4	2.7	4.4
Oesophagitis, GERD, peptic ulcer disease, gastritis, duodenitis	**<0.001**	3.0	2.2	4.1
Cardiac arrhythmia	**<0.001**	2.0	1.7	2.5
Obesity	0.006	1.9	1.2	3.1
Pelvic injury	**<0.001**	1.9	1.6	2.3
Mental disorder	**<0.001**	1.8	1.6	2.1
Mild hypokalemia	**<0.001**	1.7	1.5	1.9
Thoracic injury	**<0.001**	1.7	1.4	2.0
Congestive heart failure	0.043	1.6	1.01	2.5
Chronic pulmonary disease	**0.003**	1.5	1.2	2.0
Cerebrovascular disease	0.018	1.4	1.1	1.9
Abdominal injury	**0.001**	1.4	1.2	1.7
Spinal column injury	**<0.001**	1.4	1.2	1.6
Diseases of the musculosceletal and connective tissue system	**<0.001**	1.3	1.2	1.5
Chronic renal disease	0.075	1.3	0.97	1.8
Sex (Male)	**<0.001**	1.3	1.1	1.4
Malignancy	0.097	1.2	0.97	1.5
Hypertension	0.019	1.2	1.03	1.4
Age	**<0.001**	1.009	1.006	1.013
Head injury	0.010	0.85	0.74	0.96

CI, confidence interval; GERD, gastro-esophageal reflux disorder, OR, odds ratio

Table 6
Predictors for length of stay

	Standard Beta	P Value	95% CI	
Hypokalemia	0.237	**<0.001**	4.1	4.9
Age	0.035	**0.003**	0.01	0.02
Sex	0.062	**<0.001**	0.7	1.5
Spinal column injury	0.072	**<0.001**	1.3	2.4
Pelvic injury	0.156	**<0.001**	4.7	6.1
Thoracic injury	0.062	**<0.001**	1.0	2.0
Abdominal injury	0.102	**<0.001**	2.6	4.0
Cardiac arrhythmia	0.065	**<0.001**	1.5	2.9
Congestive heart failure	0.034	**0.001**	1.1	4.4
Chronic pulmonary disease	0.111	**<0.001**	5.1	7.4
Cerebrovascular disease	0.029	0.005	0.4	2.6
Diseases of the musculosceletal and connective tissue system	0.104	**<0.001**	1.8	2.7
Malignancy	0.029	0.005	0.3	1.9
Obesity	0.061	**<0.001**	3.5	7.0
Chronic renal disease	0.022	0.038	0.1	2.2

Discussion

The aims of our study were (1) to determine the prevalence of hypokalemia, (2) to evaluate predictors for hypokalemia, and (3) to show the influence of hypokalemia on in-hospital outcome in trauma patients. We found that one third of all in-hospital patients after trauma suffered hypokalemia. Risk factors were congestive heart failure, trauma to the visceral cavities (especially head), and spinopelvic injuries. Hypokalemia, especially moderate to severe hypokalemia, was significantly associated with adverse events, length of stay and mortality.

The strengths of this study are the large sample size and the comprehensive assessment of comorbidities and complications. However, the findings from this study may not be generalizable to all hospitals across Switzerland because this study was carried out in an university hospital. Confirmation from other small, nonacademic and/or rural institutions is needed. In addition, there are certain limitations that should be accounted for in this retrospective database study. First, our data are based on billings from ICD-10 codes, and such a coding system may be limiting and inaccurate.[15] Second, retrospective analysis of a large database of in-hospital patients may result in possible reporting discrepancies and coding errors.[16] Last, there is a lack of information about drugs (e.g., antibiotics, diuretics, laxatives, ace – inhibitors, insulin) influencing the plasma potassium level.

Hypokalemia was present in 33% of all adult trauma patients admitted to our Level I trauma center. This is coherent with previous literature, reporting up to 50% of trauma patients presenting with hypokalemia.[1-3] It was diagnosed most of the time at admission or one day after. Several studies, mainly in patients with head trauma, showed that changes of potassium concentration occur within the first 24 hours after admission.[17-20] Wu et al. showed, that hypokalemia mainly occurred in the first 24-96 hours after traumatic brain injury.[2]

Congestive heart failure was plausibly associated with hypokalemia, while chronic renal diseases were protective. Major trauma, especially head trauma, was a risk factor for hypokalemia. Beal et al. reported that hypokalemia on arrival was more frequent in trauma patients with head injuries. They showed that patients with severe hypokalemia (< 3.1 mmol/L) had lower GCS at admission than those who had mild hypokalemia (3.4 – 3.5 mmol/L). Furthermore, they reported that the average age of patients with hypokalemia was significantly lower than those without hypokalemia.[3] Similar, Ookuma et al. showed that patients presenting with hypokalemia (< 3.5mmol/L) had significantly more often a craniotomy as a surrogate of the severity of head trauma.[1]

Hypokalemia was associated with a negative in-hospital outcome. Wu et al. analyzed head trauma patients only and reported that the mortality in patients with severe hypokalemia was higher (78.4%) than those with moderate (26.1%) or mild (13.3%) hypokalemia.[2] Although Beal et al. revealed that there was no statistically significant difference in mortality when comparing the severe, moderate, and mild hypokalemia groups in trauma patients,[3] the population of their study was heterogeneous, which may produce selection bias.[2] Interestingly, Norring-Agerskov et al. reported that hypokalemia was not a predictor for mortality in their large hip fracture study.[21] However, they looked at potassium level at admission only. We found, that in some patients hypokalemia was not present at admission, however, later in the course.

There have been a few studies about potassium level abnormalities in trauma patients to elucidate its pathophysiology.[22-24] Zavagli et al. measured a lower potassium level in 123 patients with an injury or surgery of the liver in contrast to patients without a liver injury. The authors considered the higher amount of adrenergic endings in the liver as a possible cause for the hypokalemia because norepinephrine leads, via stimulation of beta-adrenergic receptors, to a potassium shift into the cells. They also postulated an accessory role of aldosterone.[22] Desborough listed a number of hormonal changes (e.g., insulin decrease; glucagon, cortico- and mineralocorticoids increase) occurring in response to trauma and surgery. These hormonal changes clearly influence the water and salt metabolism.[23] Vanek et al. prospectively studied 133 trauma patients and found age, arterial pH, and serum epinephrine level as significant predictors for hypokalemia at admission.[24]

Hypokalemia is mostly an indicator of major trauma (stress) or the consequence of some comorbidities and medications. Hypokalemia should be recognized. In these circumstances, the hypokalemia is usually present at admission and a clear marker of mortality. The more severe and the later a hypokalemia was present during hospitalization the higher was the risk of complications. However, hypokalemia is often neglected or self-corrected within a few days.

Overall, the major goal of the treatment should be the management of the underlying disease or elimination of the causative factor. Therefore, strategies aimed at achieving and maintaining normokalemia must take into account factors such as (1) baseline potassium values, (2) the presence of underlying medical conditions such as congestive heart failure, (3) the use of medications that alter potassium levels (eg, non-potassium-sparing diuretics), (4) patients variables such as diet and salt intake, and (5) the ability to adhere to a therapeutic regimen.[25] Importantly, any treatment that is associated with a risk of hypokalemia requires regular monitoring of potassium, but currently it is not possible to provide evidence-based guidelines for frequency of monitoring and cut-off values for intervention.[26]

The questions remain if hypokalemia is just a surrogate of trauma severity (and consecutively a higher morbidity and mortality rate) and correction of this electrolyte balance may decrease the negative effects. Internal guidelines and educational activities in five Swiss hospitals helped to increase the rate of potassium normalization during hospital stay and as a consequence also reduced the length of stay.[27] We conclude that hypokalemia is a common finding, a modifiable risk factor for negative outcome, and must be measured and addressed.

Ethical statement

Compliance with Ethical Standards: All authors comply with ethical standards.

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Ethical approval

This study was approved by the cantonal ethical review board (KEK-ZH-No. 2011-0382, PB_2016_01888).

Author contribution statement

Käch I, Beeler P: literature search, data collection, writing;
Schlögl M, Pape HC: literature search, data interpretation, writing, critical revision;
Neuhaus V: study design, data collection, data analysis, data interpretation, critical revision.

Declaration of Competing Interest

The authors have no conflict of interest with this study

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sipas.2021.100041.

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